as evidenced by Nachman, U.S. Patent No. 5,714,150 ("Nachman"). According to the Examiner:

> "Lockwood teaches agglomerated granular protein-rich nutritional supplements, for use by specific groups of individuals. Lockwood teaches that one group to be treated include [sic] postmenopausal women, who are particularly susceptible to osteoporosis, and teaches supplements designed for women. The supplements may comprise edible plant extracts, including olive leaf extract. Olive leaf extract is know to inherently contain oleuropein; as evidence Nachman teaches a method of producing olive leaf extract known as oleuropein with valuable medicinal properties. Therefore, one skilled in the art of edible plant extracts would envisage oleuropein from the disclosure of "olive leaf extract" in Lockwood.
>
> "Lockwood does not specifically teach that the supplement comprising olive leaf extract inhibits bone resorption
>
> "However, it would have been obvious to a person having ordinary skill in the art at the time the invention was made to use the supplement taught by Lockwood to treat bone resorption; thus arriving at the claimed invention. One skilled in the art would be motivated to do so because Lockwood fairly teaches and suggests supplements for women, including women susceptible to osteoporosis, and Lockwood also fairly teaches and suggests the incorporation of edible plant extracts, including olive leaf extract, in said supplements. Thus one of skill in the art would be motivated to select the use of olive leaf extract in the supplement for women by routine experimentation, in order to optimize the intended use of the resulting supplement, which includes making women less susceptible to osteoporosis, thereby inhibiting bone resorption."

(Office Action, pp. 4-5, citations omitted). Applicants respectfully traverse this rejection.

Lockwood is drawn to different protein-rich nutritional supplements for use by specific groups of individuals (*Abstract*), including women and older adults (*col. 1, lines 25-29*). Lockwood further teaches that nutritional needs of women, in particular of osteoporosis-susceptible postmenopausal women (*col. 1, lines 37-38*), are different from those of men (*col. 1, lines 30-31*). Lockwood describes many compounds which are supposed to help maintaining healthy bones:

- vitamin D (*cf. column 2, lines 28-30*), which assists in the mineralization and calcification of bones and prevent osteomalacia in adults;

- calcium (*col. 3, lines 61-63*), which helps building bones and teeth;

- magnesium (*col. 4, lines 1-3*), which helps preventing osteoporosis and bone loss;

- manganese (*col. 4, lines 5-7*), which assists in bone growth and helps preventing osteoporosis;

- boron (*col. 4, lines 17-19*), which helps maintaining healthy bones and allows an increased absorption of both calcium and magnesium; and

- soy isoflavones (*col. 4, lines 45-47*), which are alleged to reverse osteoporosis.

Many of the nutritional supplements of Lockwood comprise edible plant extracts, which have been shown to exhibit many different beneficial physiological effects (*col. 3, lines 30-59 and column 4, lines 30-52*). Soy isoflavones are the only edible plant extracts which Lockwood identifies as useful for treating osteoporosis or any other bone disease (*col. 4, lines 45-47*). Olive leaves are only mentioned only once in Lockwood, as part of a long list of plants suitable for use in Lockwood's nutritional supplements (*col. 9, lines 28-41*).

Lockwood provides many examples of nutritional supplements, one of which is specifically designed for women (*col. 13, line 38 – col. 14, line 39*) and another one of which is specifically designed for older adults (*col. 18, line 38 – col. 19, line 20*):

- the nutritional supplement for women comprises approximately 0.2 to 9% by weight of edible plant extracts, which are preferably cranberry extracts, dong quai, evening primrose oil (GLA), β-carotene and/or colosolic acid (*col. 13, lines 59-62*); the use of olive leaf extract is not described;

- the nutritional supplement for older adults does not comprise any edible plant extracts.

Nachman is drawn to a method for extracting oleuropein from olive leaves (*cf. col. 1, lines 1-2*). The final dry powder extract only comprises about 35% by weight oleuropein (*col. 2, lines 58-61*). Nachman teaches that oleuropein has valuable medicinal properties, in particular an antiviral activity and an antioxidant activity (*col. 1, lines 1-40*). However, Nachman provides no teachings that oleuropein might be used to stimulate bone formation and/or inhibit bone resorption and/or treat osteoporosis.

Nothing in Lockwood teaches or suggests that indicate that olive leaf extracts, which are mentioned only once in Lockwood, are helpful for treating osteoporosis; nor does Nachman, which makes no mention of osteoporosis, cure this deficiency. Olive leaves are only one of the many plants identified as suitable for use in the nutritional supplements of Lockwood. In fact, many of the nutritional supplements of Lockwood comprise edible plant extracts which are specifically exemplified in Lockwood: caffeine, β-carotene, yohimbine, cranberry extracts, dong quai, evening primrose oil (GLA), colosolic acid and *Mucuna pruriens*. Olive leaf extracts are never exemplified.they are only mentioned once and their use is not exemplified.

There is no indication in Lockwood that the nutritional supplement for women is designed for young or older women, or whether it is designed for pre- or postmenopausal women (*col. 13, lines 37-40*). Furthermore, the extensive list of preferred edible plant extracts suitable for use in the nutritional supplement for women does not include olive leaf extracts (*col. 13, lines 59-62*) . Thus, Lockwood does not teach or suggest the use of including olive leaf extracts in nutritional supplements for women. Moreover, the nutritional supplement for older adults does

not comprise any edible plant extracts, much less olive leaf extract (*col. 18, lines 38-53*).

It is well known that osteoporosis more specifically affects older adults, and in particular older women. Thus, Lockwood cannot be said to teach or suggest the use of olive leaf extract (or oleuropein) in composition for the treatment of osteoporosis and/or the inhibition of bone resorption and/or stimulation of bone formation..

Moreover, Lockwood describes many compounds which are supposed to help maintaining healthy bones, in particular preventing or treating osteoporosis. Said compounds are vitamin D, calcium (*col. 3, lines 60-62*), magnesium (*col. 4, lines 2-3*), manganese (*col. 4, lines 5-7*), boron (*col. 4, lines 17-18*) and soy isoflavones (*col. 4, lines 45-47*). However, Lockwood does not describe olive leaf extract as useful for the purpose of preventing or treating osteoporosis.

Therefore, a person of skill in the art seeking to design a nutritional supplement for treating osteoporosis would be led by Lockwood to select calcium, magnesium, vitamin D, boron, manganese and/or soy isoflavones, to incorporate into a protein-rich nutritional supplement. He or she would be not be led to choose olive leaf extracts to treat osteoporosis. Nor would Nachman cure this deficiency, as Nachman - which is aimed at a new method for extracting oleuropein from olive leaves to be used for its anti-bacterial and anti-viral activities - does not teach or suggest the use of oleuropein for the treatment of osteoporosis.[1]

In view of the foregoing, applicants respectfully submit that claim 1 would not have been obvious over Lockwood in view of Nachman; nor would any of the

[1] In fact, olive leaf extracts are very complex mixtures comprising many other compounds in addition to oleuropein. Indeed, oleuropein represents only 35% by weight of the final dry powder extract of Nachman (*col. 2, lines 42-44*).

dependent claims have been obvious either. Accordingly, applicants request reconsideration and withdrawal of this rejection.

Rejection over Hamdi in view of Katori

The Examiner has also rejected claims 1, 16, 18-19, and 21-23 under 35 U.S.C. § 103(a) as allegedly unpatentable over Hamdi, et al., U.S. Patent Application Publication US 2003/0004117 ("Hamdi") in view of Katori, et al., Inflamm. Res. 49 (2000), pp. 367-392 ("Katori"). Applicants traverse this rejection.

Hamdi is drawn to methods for efficiently inhibiting angiogenesis, and for treating different inflammatory diseases associated with unwanted angiogenesis (¶¶ *[0056] – [0071]*. In a preferred embodiment, the administered compound is oleuropein, in particular oleuropein from the olive tree (¶ *[0054]*.

Katori is a general review article about cyclooxygenase-2 (COX-2). COX-2 has been reported in many tissues, both in physiological and pathological states. It plays a role in many phenomena, for example in different inflammation states, in arthritis, in gastric ulcer, in colon cancer, in hyperalgesia, in Alzheimer's disease and in some states of the kidney, brain and female reproductive organs, but also in angiogenesis and in bone absorption (*Abstract*). In the section of the article relating to the role of COX-2 in bone absorption (*p. 373*), Katori reports that prostaglandins, whose formation is catalysed by COX-2, could be responsible for hypercalcemia and inflammatory bone loss in periodontal diseases and in rheumatoid arthritis. The main effect of prostaglandins, in particular of one thereof, could be the stimulation and inhibition of bone resorption and formation (*Id.)*.

Hamdi teaches the use of oleuropein for inhibiting angiogenesis and treating different inflammatory diseases associated with unwanted angiogenesis, whereby the described activity of oleuropein is basically focused on angiogenesis in itself. Despite identifying dozens of conditions which its method might be useful in treating,[2] Hamdi does not describe the use of oleuropein or of any of the derivatives thereof for treating osteoporosis.

Simply put, a person of skill in the art seeking to treat osteoporosis would not look to Hamdi, which despite mentioning a plethora of health conditions, is completely silent with respect to the treatment of osteoporosis.

Applicants respectfully suggest that the Examiner's reliance on Hamdi is based on hindsight reasoning, which the Examiner would agree is improper. Drawing on knowledge of the claimed invention, when the prior art does not contain or suggest that knowledge, is using the invention as a template for its own reconstruction, which is not permitted.

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[2] Including diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma and retrolental fibroplasia, epidemic keratoconjunctivitis, vitamin A deficiency, contact lens overwear, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phylectenulosis, syphilis, Mycobacteria infections, lipid degeneration, chemical burns, bacterial ulcers, fungal ulcers, Herpes simplex infections, Herpes zoster infections, protozoan infections, Kaposi sarcoma, Mooren ulcer, Terrien's marginal degeneration, marginal keratolysis, trauma, rheumatoid arthritis, systemic lupus, polyarteritis, Wegeners sarcoidosis, Scleritis, Steven's Johnson disease, periphigoid radial keratotomy, and corneal graph rejection (¶ [0060]), diabetic retinopathy, macular degeneration, sickle cell anemia, sarcoid, syphilis, pseudoxanthoma elasticurn, Pagets disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis/vitritis, mycobacterial infections, Lyme's disease, systemic lupus erythematosis, retinopathy of prematurity, Eales disease, Bechets disease, infections causing a retinitis or choroiditis, presumed ocular histoplasmosis, Bests disease, myopia, optic pits, Stargarts disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, trauma and post-laser complications. Other diseases include, but are not limited to, diseases associated with rubeosis (neovascularization of the angle) and diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue, including all forms of proliferative vitreoretinopathy, whether or not associated with diabetes (¶ [0060]), inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, psoriasis, sarcoidosis and rheumatoid arthritis ([¶0062]), and a wide variety of cancers, including lung, colon, breast, ovarian, prostate and hepatic tumor cells as well as squamous cell carcinomas such as pharynx, colon, rectal, pancreatic, stomach, liver, lung, breast, skin, prostate, ovary, cervical, uterine and bladder cancers; leukemias; lymphomas; gliomas; retinoblastomas; and sarcom

Katori is a review article drawn to the COX-2 protein, which Katori reports is said to be involved in bone absorption. However, bone absorption and osteoporosis are complex phenomena, involving many other proteins and effectors besides COX-2. Indeed, many reviews, such as the one by Shen et al. published in Current Mol. Med. 3(8):737-57 (2003), focus on the many molecular mechanisms of osteoporosis. Therefore, a person or ordinary skill in the art seeking a treatment for osteoporosis would not have specifically focused on COX-2, which is only one of the many molecular effectors in the process of osteoporosis.

Even if a person of ordinary skill in the art had used Katori and selected COX-2 as a target for treating osteoporosis, Katori, there is no reason why such a person would have looked to combined Katori's teachings with those of Hamdi. Katori teaches that COX-2 is involved in many other phenomena than bone adsorption. These phenomena include different inflammation states, arthritis, gastric ulcer, colon cancer, hyperalgesia, Alzheimer's disease, some states of the kidney, brain and female reproductive organs, and angiogenesis. Angiogenesis is therefore only one particular state in which COX-2 is involved, amongst many others.

A person of ordinary skill in the art might have looked for compounds that are said to be efficient in the same phenomena as bone adsorption, but not in angiogenesis only. Moreover, it is well known that the responses or behaviours of the human or animal body are very complex and involve many effectors and pathways. Angiogenesis itself is a very complex phenomenon, with many alleged inhibitors having multiple modes of action. According to Clarke et al. (in Aust. Prescr. 29:9-12 (2006)), "the successful inhibition of angiogenesis may involve the combination of multiple drugs with differing modes of action".

In conclusion, there are so many compounds which have been reported as being efficient in physiological phenomena in which COX-2 is involved that it is not proper to assert that it would have been obvious for the man skilled in the art to specifically select oleuropein from Hamdi for treating osteoporosis, since Hamdi does not describe or even mention the use of oleuropein or of any of its derivatives for treating osteoporosis.

Moreover, even if a person of ordinary skill in the art seeking active compounds for treating osteoporosis started from Katori, that person would have first focused on compounds described as COX-2 inhibitors. However, suitable COX-2 inhibitors described in Katori are NSAIDS, the chemical structures of which are very different from oleuropein and the derivatives thereof. Furthermore, the target compound(s) of oleuropein and the action process(es) thereof are not described in Hamdi, and nothing is reported on a possible interaction between oleuropein and COX-2. Therefore, even if the man skilled in the art had selected Hamdi, there is no indication that oleuropein and the derivatives thereof could be NSAIDs inhibiting COX-2. Consequently, it would not have been obvious for a person of skill in the art to have selected oleuropein to test for its activity relative to osteoporosis, much less obvious to have arrived at the claimed invention.

Consequently, applicants submit that the obviousness rejection over Hamdi in view of Katori should be reconsidered and withdrawn.

Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance, and earnestly solicit prompt notice to that effect. Should the Examiner believe a personal interview would be helpful in advancing prosecution, he is invited to telephone the undersigned.

Respectfully submitted,

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